

CLAIM AMENDMENTS

1. (Original) A protein complex comprising
 - (a) a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group consisting of:
 - (i) Sambiasin-1 (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of Sambiasin-1 encoded by a nucleic acid that hybridizes to the Sambiasin-1 nucleic acid or its complement under low stringency conditions,
 - (b) and at least one second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of:
 - (i) Presenilin-1 (SEQ ID No: 2), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of Presenilin-1 encoded by a nucleic acid that hybridizes to the Presenilin-1 nucleic acid or its complement under low stringency conditions,
 - (ii) Nicastrin (SEQ ID No: 3), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of Nicastrin encoded by a nucleic acid that hybridizes to the Nicastrin nucleic acid or its complement under low stringency conditions, wherein said first protein and said second protein are members of a native cellular complex, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
2. (Original) A protein complex comprising Sambiasin-1 (SEQ ID No: 1) or Sambiasin-2 (SEQ ID No: 4) and Presenilin-1 (SEQ ID No: 2) or Presenilin-2 (SEQ ID No: 5).

3. (Currently Amended) A protein complex according to ~~claims 1 or 2~~ claim 1 further comprising Nicastrin (SEQ ID No: 3)

4. (Currently Amended) A protein complex according to ~~any of claims 1 to 3~~ claim 1 comprising Sambiasin-1 (SEQ ID No: 1) and Presenilin-1 (SEQ ID No: 2) and Nicastrin (SEQ ID No: 3).

5. (Currently Amended) The complex of ~~any claims 1 to 4~~ claim 1 comprising a functionally active derivative of any of the proteins of said complex, wherein the functionally active derivative is a fusion protein comprising said protein fused to an amino acid sequence different from said protein.

6. (Original) The complex of claim 5 wherein the functionally active derivative is a fusion protein comprising said protein fused to an affinity tag or label.

7. (Currently Amended) The complex of ~~any claims 1 to 4~~ claim 1 comprising a fragment of any of the proteins of said complex, which fragment binds to another protein component of said complex.

8. (Currently Amended) The complex of ~~any claims 1 to 7~~ claim 1 that is involved in the gamma-secretase activity.

9. (Currently Amended) A protein comprising the amino acid sequence of SEQ ID No: 1, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of Sambiasin-1 encoded by a nucleic acid that hybridizes to the Sambiasin-1 nucleic acid or its complement under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X

SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C, with the proviso that the protein does not have the amino acid sequence according to SEQ ID No: 6.

10. (Original) Protein comprising the amino acid sequence of SEQ ID No: 1.
11. (Currently Amended) A nucleic ~~Nucleic~~ acid encoding a protein according to ~~claims 9 or 10~~ claim 9.
12. (Currently Amended) A construct ~~Construct, preferably a vector construct,~~ comprising
 - (a) a nucleic acid according to claim 11 and at least one further nucleic acid which is normally not associated with said nucleic acid, or
 - (b) at least two separate nucleic acid sequences each encoding a different protein, which protein is selected from the group consisting of Sambiasin-1 (SEQ ID No: 1), Presenilin-1 (SEQ ID No: 2), and Nicastrin (SEQ ID No: 3) ~~of any of the proteins~~, or a functionally active fragment or a functionally active derivative thereof ~~according to claim 1~~.
13. (Currently Amended) A host cell ~~Host cell,~~ containing ~~a vector comprising at least one of the nucleic acids of claim 11 and/or any of the constructs of claim 12 or containing several vectors each one or more constructs according to claim 12 comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to claim 1.~~
14. (Currently Amended) An antibody or a fragment of said antibody containing the binding domain thereof, which binds the complex of claim 1, ~~any claims 1 to 8~~ and which does not bind the first protein when uncomplexed or the second protein when uncomplexed ~~and/or an antibody or a fragment of said antibody containing the binding domain thereof which binds to any of the group of proteins according to any of claims 9 or 10.~~

15. (Currently Amended) A kit comprising in one or more containers ~~container~~ the complex of claim 1 ~~any of claims 1 to 8 and/or the proteins of any of claims 9 or 10,~~ optionally together with ~~an antibody according to claim 14 and/or further components such as~~ reagents and working instructions.

16. (Currently Amended) A kit according to claim 15 for the diagnosis or prognosis of a disease or a disease risk, ~~preferentially for a disease or disorder such as~~ wherein the disease is selected from the group consisting of neurodegenerative diseases, ~~such as Alzheimer,~~ and developmental disorders caused by defects in the Notch pathway.

17. (Currently Amended) An array ~~Array,~~ comprising the ~~in which at least a~~ complex according to ~~any of claim 1 to 8 and/or any of the proteins of any of claims 9 or 10~~ and/or at least one antibody according to claim 14 is attached to a solid carrier.

18. (Currently Amended) A method ~~process~~ for processing the physiological substrates of ~~any of the complexes of any of claims 1 to 4~~ the complex of claim 1 comprising the step of bringing into contact the complex ~~a complex of any of claims 1 to 7~~ with said substrate, such that said substrate is processed.

19. (Currently Amended) A pharmaceutical composition comprising the protein complex of claim 1 ~~any claims 1 to 8~~ and a pharmaceutically acceptable carrier ~~and/or any of the proteins of claims 9 or 10 and a pharmaceutically acceptable carrier.~~

20. (Currently Amended) A pharmaceutical composition according to claim 19 for the treatment of diseases and disorders, wherein the disease or disorder is selected from the group consisting of ~~such as~~ neurodegenerative diseases, ~~such as Alzheimer, and/or and~~ developmental disorders caused by defects in the Notch pathway.

21. (Currently Amended) A method for screening for a molecule that binds to the complex of claim 1 ~~anyone of claims 1 to 8 and/or any of the proteins of claims 9 or 10,~~ comprising the following steps:

- (a) exposing said complex ~~or protein~~, or a cell or organism containing same, to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the complex ~~or protein~~.

22. (Currently Amended) A method for screening for a molecule that modulates ~~directly or indirectly~~ the function, activity, composition or formation of the complex of ~~any one of claims 1 to 8~~ claim 1 comprising the steps of:

- (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
- (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

23. (Original) The method of claim 22 wherein the amount of said complex is determined.

24. (Original) The method of claim 22, wherein the activity of said complex is determined.

25. (Currently Amended) The method of claim 24, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with

a physiological substrate of the complex of any of the complexes according to any of claims 1 to 4 and determine whether said substrate is processed.

26. (Original) The method of claim 22, wherein the amount of the individual protein components of said complex are determined.

27. (Original) The method of claim 26, wherein said determining step comprises determining whether

(i) Sambiasin-1 (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of Sambiasin-1 encoded by a nucleic acid that hybridizes to the Sambiasin-1 nucleic acid or its complement under low stringency conditions, and/or

(ii) Presenilin-1 (SEQ ID No: 2), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of Presenilin-1 encoded by a nucleic acid that hybridizes to the Presenilin-1 nucleic acid or its complement under low stringency conditions, and/or

(iii) Nicastrin (SEQ ID No: 3), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of Nicastrin encoded by a nucleic acid that hybridizes to the Nicastrin nucleic acid or its complement under low stringency conditions,

are present in the complex and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

28. (Currently Amended) The method of ~~any of claims 22 to 27~~ claim 22, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, wherein the disease or disorder is selected from the group consisting of

~~such as neurodegenerative diseases, such as Alzheimer,~~ and developmental disorders caused by defects in the Notch pathway.

29. (Currently Amended) A method of manufacturing a medicament comprising the use Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of ~~any one of claims 1 to 8~~ claim 1 to manufacture a medicament for the treatment or prevention of a disease or disorder, wherein the disease or disorder is selected from the group consisting of ~~such as neurodegenerative diseases, such as Alzheimer,~~ and developmental disorders caused by defects in the Notch pathway.

30. (Currently Amended) A method for the production of a pharmaceutical composition comprising carrying out the method of ~~any of claims 22 to 27~~ claim 22 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

31. (Currently Amended) A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, component composition of, or intracellular localization of the complex of ~~any one of claims 1 to 8~~ claim 1, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

32. (Original) The method of claim 31, wherein the amount of said complex is determined.

33. (Original) The method of claim 31, wherein the activity of said complex is determined.

34. (Currently Amended) The method of claim 33, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a physiological substrate of ~~any of the complexes~~ complex, ~~according to any of claims 1 to 4~~ and determine whether said substrate is processed.

35. (Original) The method of claim 31, wherein the amount of the individual protein components of said complex are determined.

36. (Original) The method of claim 35, wherein said determining step comprises determining whether

(i) Sambiasin-1 (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of Sambiasin-1 encoded by a nucleic acid that hybridizes to the Sambiasin-1 nucleic acid or its complement under low stringency conditions, and/or

(ii) Presenilin-1 (SEQ ID No: 2), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of Presenilin-1 encoded by a nucleic acid that hybridizes to the Presenilin-1 nucleic acid or its complement under low stringency conditions, and/or

(iii) Nicastrin (SEQ ID No: 3), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of Nicastrin encoded by a nucleic acid that hybridizes to the Nicastrin nucleic acid or its complement under low stringency conditions,

are present in the complex and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of

2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1 % SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

37. (Currently Amended) ~~The complex of any one of claims 1 to 8, or proteins of any of claims 9 or 10 or the antibody or fragment of claim 14, for use in a method of diagnosing a disease or disorder such as~~ The method of claim 31, wherein the disease or disorder is selected from the group consisting of neurodegenerative diseases such as Alzheimer and developmental disorders caused by defects in the Notch pathway.

38. (Currently Amended) A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of ~~anyone of claims 1 to 8~~ claim 1 comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity of, or protein components of, said complex.

39. (Original) The method according to claim 38, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

40. (Original) The method according to claim 39, wherein said disease or disorder involves increased levels of the amount or activity of said complex.

41. (Cancelled)

42. (New) An antibody or a fragment of said antibody containing the binding domain thereof, which binds to the protein of claim 9.

43. (New) A kit comprising in one or more containers the protein of claim 9, optionally together with reagents and working instructions.

44. (New) The kit of claim 15, which further comprises a protein comprising the amino acid sequence of SEQ ID No: 1, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof

45. (New) The kit of claim 15, which further comprises an antibody or a fragment of said antibody containing the binding domain thereof, which binds the complex.

46. (New) An array comprising the protein of claim 9 attached to a solid carrier.

47. (New) An array comprising at least one antibody according to claim 14 attached to a solid carrier.

48. (New) A pharmaceutical composition comprising the protein of claim 9 and a pharmaceutically acceptable carrier.

49. (New) A method for screening for a molecule that binds to the protein of claim 9 comprising the following steps:

- (a) exposing said protein, or a cell or organism containing same, to one or more candidate molecules; and
- (b) determining whether said candidate molecule is bound to the protein.